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Efficient and rapid experimental procedure for the synthesis of furan diol from D-glucal using ionic liquid

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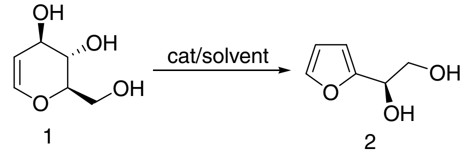
Abstract—A new efficient and rapid experimental method and product isolation procedure as well as easy recyclable reaction media is expected to contribute to the development of a green strategy for the synthesis of furan diol from D-glucal. We determine the best conditions of reaction, minimizing the toxicity and finding an environmentally more acceptable process, using [Bmim][MSO_4]/$InCl_3 \cdot 3H_2O$ as a new solvent system under extremely mild conditions, providing high yields with a dramatic enhancement of reaction rate.

2-(D-glycero-1,2-dihydroxyethyl)furan (**2**) is a potential chiral building block used as an intermediate in the organic synthesis of biologically significant products.[1,2] Monosaccharides are extremely acid-labile and under hydrolytic conditions lead to furans. Thus, in 1966 the first transformation of D-glucal (**1**) to optically active furan diol **2** (Scheme 1) was reported, using H_2O/HOAc at 170 °C of temperature in moderate yield (50%).[3,4]

Similarly, in 1975 this transformation obtained the highest yield for catalysis by toxic metal salt $HgSO_4$ in concentrated H_2SO_4; its possible mechanism of elimination was also discussed.[5] Subsequently, by using $Sm(OTf)_3$ or $RuCl_2(PPh_3)_3$ in the presence of H_2O, which requires relatively higher temperature (80–100 °C), the researchers suggested the probable nucleophilic attack of H_2O on D-glucal, opening of pyranose ring followed by cyclization to a five-membered ring and dehydration furnished the furan ring.[6] More recently, relatively less toxic and efficient catalysts have been reported.[7] The use of $InCl_3 \cdot 3H_2O$ on D-glucal or its epimer D-galactal in acetonitrile for 2.5 h at room temperature led to the same product **2** in 82% yield.



Scheme 1.

At present, this reaction continues receiving wide attention. Thus, in 2004 perchloric acid supported on silica gel as a new reagent system was introduced,[8] but during this reaction there appeared to be some furan diol racemization. Finally in 2005, montmorillonite KSF clay in acetonitrile for 5–7 h at room temperature was reported as a promoter for the conversion of glycals into furan diols with high selectivity,[9] searching for environmental compatibility and recyclable catalyst.

All of these synthetic procedures explained above have been carried out or worked-up in classical volatile organic compounds (VOCs) such as dichloromethane, acetonitrile, ethyl acetate, hexane and methanol. However, in recent times, the room temperature ionic liquids (RTILs) have a significant interest as new solvents in the area of green synthesis.[10,11] They have emerged as a set of green designer solvents with unique properties such as negligible vapour pressure, tuneable polarity, high thermal stability and they can be easily recycled without any significant loss of activity. They are excellent media for catalytic processes[12] and it has been demonstrated that some reactions in RTILs show rate acceleration and increased yield compared to VOCs.[13]

Keywords: Diols; Ionic liquids; Furans; Green-chemistry; Solvent effects.

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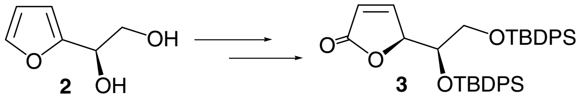
In view of the emerging importance of the RTILs used as solvent systems,[14] as novel alternative reaction media for the immobilization of transition metal based catalysts and Lewis acids,[15] or more recently as clean reagent and catalyst,[16] our purpose in this Letter is to explore the effect of RTILs for the synthesis of 2-(D-glycero-1,2-dihydroxyethyl)furan **2** from D-glucal.

As part of our ongoing program on the synthesis of natural products using the oxidation of a furan ring with singlet oxygen, we used chiral furan diol **2** as starting material towards the synthesis of optically active butenolide **3**[17] (Scheme 2).

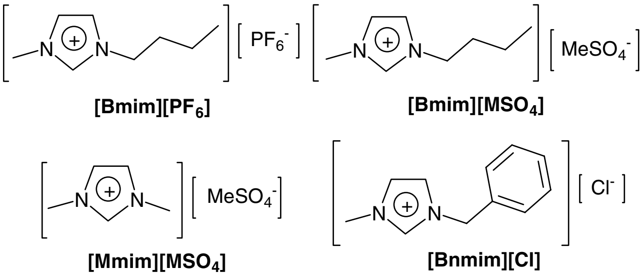
In our laboratory we synthesized **2** using D-glucal in the presence of 10% $InCl_3 \cdot 3H_2O$ in acetonitrile at room temperature.[7]

We selected the following RTILs: 1-butyl-3-methylimidazolium hexafluorophosphate [Bmim][PF_6], 1-butyl-3-methylimidazolium methylsulfate [Bmim][MSO_4], 1,3-dimethylimidazolium methylsulfate [Mmim][MSO_4], 1-benzyl-3-methylimidazolium chloride [Bnmim][Cl]. All these were synthesized and characterized in our laboratories[18,19] (Scheme 3).

In a first study, the influence of RTILs in this transformation as catalyst promoter was established. We used 10% $InCl_3 \cdot 3H_2O$ and acetonitrile as catalyst and solvent respectively at room temperature, under synthetic procedures reported in the literature;[7] nevertheless, an additional catalytic amount of RTIL (10%) was included (entries 2–5; *General procedure 1*).[20] The spectral data of furan diol **2** were in accordance with the reported data.[7]



Scheme 2.



Scheme 3. RTILs structures with cations imidazolium derivatives.

The results presented in Table 1 show a dramatic enhancement of the transformation rate of D-glucal to optically active furan diol **2**, compared to the method reported without ionic liquids[7] (entry 1) or to any other classical procedures;[3–6,8] besides similar high yields were obtained (73–78% yields). It should be noticed that the reaction time was reduced by 5 times with [Bmin][PF_6] (entry 2) and it was possible to reduce it up to 15 times with [Bnmim][Cl] (entry 5). However, the fastest reaction rate was observed with methylsulfate derivatives (entries 3 and 4), where the transformation was almost instantaneous in both RTILs. Therefore, we can say that this new synthetic procedure described above—using RTILs—contribute to better results of reaction rate than the procedures previously reported, under extremely mild conditions and high yields.

On the other hand, we explored the absence of $InCl_3 \cdot 3H_2O$ to establish the potential catalysis use of RTILs in this reaction (entries 10–13; *General procedure 2*).[21] The results clearly show an absence of catalytic effect, even maintaining 48 h of reaction time.

Next, in order to evaluate RTILs as recyclable solvent systems in this transformation, we substituted acetonitrile for these green solvents (entries 6–9; *General procedure 3*).[22] The treatment of D-glucal with $InCl_3 \cdot 3H_2O$ (10%) in corresponding RTIL at room temperature

Table 1. Study of various RTILs in the synthesis of 2-(D-glycero-1,2-dihydroxyethyl)furan (**2**) from D-glucal

Entry	RTIL	Catalyst	Solvent	Reaction time	Yield[a] (%)
1	—	$InCl_3 \cdot 3H_2O$	CH_3CN	2 h 30 min	82
2[b]	[Bmin][PF_6]	$InCl_3 \cdot 3H_2O$	CH_3CN	30 min	73
3[b]	[Bmim][MSO_4]	$InCl_3 \cdot 3H_2O$	CH_3CN	Few seconds	78
4[b]	[Mmim][MSO_4]	$InCl_3 \cdot 3H_2O$	CH_3CN	Few seconds	77
5[b]	[Bnmim][Cl]	$InCl_3 \cdot 3H_2O$	CH_3CN	10 min	75
6[c]	[Bmim][PF_6]	$InCl_3 \cdot 3H_2O$	—	15 min	5
7[c]	[Bmim][MSO_4]	$InCl_3 \cdot 3H_2O$	—	15 min	79
8[c]	[Mmim][MSO_4]	$InCl_3 \cdot 3H_2O$	—	6 h 30 min	70
9[c]	[Bnmim][Cl]	$InCl_3 \cdot 3H_2O$	—	24 h	68
10[d]	[Bmim][PF_6]	—	CH_3CN	48 h	—
11[d]	[Bmim][MSO_4]	—	CH_3CN	48 h	—
12[d]	[Mmim][MSO_4]	—	CH_3CN	48 h	—
13[d]	[Bnmim][Cl]	—	CH_3CN	48 h	—

[a] Yield refers to isolated furan diol **2** after purification by column chromatography. The structure of product **2** was characterized by ^1H NMR and it was in accordance with the reported data.[7]

[b] According to procedure 1.[20]

[c] According to procedure 3.[22]

[d] According to procedure 2.[21]

afforded furan diol **2** in 5–79% yields. Except for the reaction in hydrophobic [Bmin][PF_6] ion liquid—which was the least efficient of all (yields 5%)—reactions of the other ionic liquids (entry 7–9) proved to have high yields, comparable to VOCs.[3–8] The instability of the PF_6^- anion towards hydrolysis in contact with moisture, forming volatiles, including HF, POF_3, etc. is well established.[23] Taking into account that indium salt must be hydrated to react as catalyst in this reaction, the above-mentioned effect undergone by hexafluorophosphate anion derivatives could be the reason of the low yield obtained in procedure 3 (entry 6; yield 5%) when compared to procedure 1 (entry 2; yield 73%). Moreover, the reaction time was reduced from 2 h 30 min, when using acetonitrile as the solvent, to 15 min when 1-butyl-3-methylimidazolium derivatives (entries 6 and 7) were used. Yet, the substitution of cation 1-butyl-3-methylimidazolium for 1,3-dimethylimidazolium (entry 8), increases the reaction time (6 h 30 min) considerably. This could be due to the fact that dimethylimidazolium cations have a more compact ionic structure than butylmethylimidazolium cations; the former being comprised of two hydrogen-bonded cation–anion chains aligned in opposite directions, hydrogen bonded together to form ribbons.[24] Probably, this effect makes RTIL's co-catalyst role difficult and so, a good connection between $InCl_3 \cdot H_2O$–RTIL is not established. Nevertheless, it should be necessary to report more examples to help us explain this special behaviour of imidazolium cations with alkyl substituents in methylsulfate derivatives. Moreover, we observed that the high viscosity of chloride derivative makes the stirring more difficult and increases the reaction time (entry 9). Thus, [Bmim][MSO_4]/$InCl_3 \cdot 3H_2O$ solvent system proved to be a more effective reaction medium for the synthesis of furan diol **2** from D-glucal by playing the dual role of the solvent as well as promoter, maintaining room temperature and high yields.

Finally, in seeking to explore the potential environmental benefits of our system, we next examined solvent recycling. The recycling of the remaining oily RTIL was possible by employing a non-aqueous work-up (simple extraction of the furan diol **2** with THF or ethyl ether) followed by removal of any traces of volatiles from RTILs in vacuo. These ionic liquids can be recycled and reused three times for subsequent reactions without any loss of activity. For example, treatment of D-glucal with [Bmim][MSO_4]/$InCl_3 \cdot 3H_2O$ afforded furandiol **2** in 79%, 77% and 77% yields over three runs. Therefore, we also avoided a chlorinated solvent (CH_2Cl_2), used in extraction process in classical procedure,[3–8] so that it could have an additional environmental benefit.

In summary, this Letter describes a new experimental method and product isolation procedure for transformation of D-glucal **1** to optically active furan diol **2**, using imidazolium RTILs. The notable feature of this procedure is the dramatic enhancement of reaction rate when RTILs are included in classical procedure with acetonitrile as the solvent. Moreover, we determined the best conditions of reaction, minimizing the toxicity and finding an environmentally more acceptable process, using [Bmim][MSO_4]/$InCl_3 \cdot 3H_2O$ as a new solvent system. This medium reaction was proved to be a more effective reaction medium for the synthesis of furan diol **2** from D-glucal **1** than the others previously reported, by playing the dual role of the solvent as well as promoter under extremely mild conditions and providing high yields.

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20. *General procedure 1*: To a stirred mixture of $InCl_3 \cdot 3H_2O$ (0.27 mmol) and RTIL (0.27 mmol) in acetonitrile, was added D-glucal (2.27 mmol) at room temperature. Stirring was continued for the appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated in vacuo. The residue was suspended into H_2O and extracted with ^{t}BuOMe. The combined organic extract was dried over Na_2SO_4, concentrated and purified by column chromatography. Yields ranged from 73% to 78%.

21. *General procedure 2*: A mixture of RTIL (2 ml) and D-glucal (2.27 mmol) in acetonitrile was stirred at room temperature. The reaction was stirred for 48 h. The absence of reaction evolution was indicated by TLC. The ionic liquid was recycled by washing with ^{t}BuOMe or THF and drying under vacuum. The combined organic extracts were concentrated to afford D-glucal.
22. *General procedure 3*: To a stirred mixture of $InCl_3{\cdot}3H_2O$ (0.27 mmol) in RTIL (2 ml), was added D-glucal (2.27 mmol) at room temperature. Stirring was continued for the appropriate time. The completion of the reaction was indicated by TLC. The residue was extracted with ^{t}BuOMe or THF. The combined organic extracts were concentrated and purified by column chromatography. Yields ranged from 5% to 80%. The ionic liquid was recycled by drying under vacuum.
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